DETAILED ACTION

Status of the claims

1. The amendment filed October 27, 2009 is acknowledged and has been entered. Currently, claims 1-56 are pending. Claims 23-31 are withdrawn as being directed to a non-elected invention. Claims 1-22 and 32-56 are under examination.

Withdrawn Rejections

2. All rejections of claims not reiterated herein, have been withdrawn.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "shortly" in claim 6 is a relative term which renders the claim indefinite. The term "shortly" is not defined by the claim, there is no definition provided for the term in the specification and the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 6 is vague and indefinite in reciting "at the latest". It is unclear if Applicant is trying to establish a range of time which incorporate a time both before and after the addition of L2. Further, it is unclear if Applicant is specifically trying to refer to the time T1. Please clarify.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-4, and 7-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Frengen (US 5,739,042) in light of Chandler et al (US 5,981,180).

Frengen discloses a method for detecting an analyte in a sample. Frengen et al disclose incubating a sample with two independently determinable forms of solid supported binding partner having affinity for the analyte and with a labelled ligand (col 3, lines 55-67, col 8, lines 48-53). Frengen disclose that the independent forms of solid support can be particles such as microparticles (e.g. col 4, col 9). Frengen discloses that the labeled ligand (R1) can be associated with a microsphere or particle (solid phase) (col 8, lines 24-38). Frengen disclose that one of the independent forms of solid support (L1 label) is associated with a specific binding partner (R2) (e.g. col 4, lines 43-51). Frengen discloses that the second form of solid support (L2 label) is associated with a specific binding partner (R3) for the analyte. Frengen discloses that the method

can be used for qualitative or quantitative measurements (e.g. col 8). Frengen discloses that the solid support (L1 label) associated with a specific binding partner (R2) requires a longer incubation than does the saturation of specific binding partner (R3) (col 5). Frengen discloses that the binding partners on the solid supports can be the same or different (col 9). Frengen discloses that the L1 and L2 supports can both be particles. Thus, Frengen is teaching the same label. Frengen discloses that the method can be a sandwich assay (e.g. col 7). Frengen discloses that the method can include the avidin/biotin system for binding to analyte or for providing for indirect detection of the analyte (col 9).

With respect to "determining an L1-dependent measurement signal at time T1 and an L2-dependent measurement signal at time T2" as instantly recited. Frengen teaches that the independently determinable forms of solid support binding partners bound with the analyte and labeled ligand are determined by flow cytometry in a gated manner (e.g. col 10, lines 20-32). Further, as shown by Chandler et al (US 5,981,180) flow cytometry requires a fluid suspension of particles in a flow down a stream in single file and passed through a examination zone in this manner to detect the individual particles (col 1, lines 55 - col 2 line 17). Thus, it is inherent that the particles of Frengen are being detected at different time intervals.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 5, 6, 19-22, 32-42, and 46-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frengen in view of Bayer et al., (The Avidin-Biotin System, Immunoassay, Chapter 11, 1996, pgs 237-267).

See above for the teachings of Frengen.

Frengen differs from the instant invention in failing to teach R3 associated with a first member of a binding pair and L2 associated with a second member of a binding pair.

Bayer et al disclose that it is known in the art of immunoassays to incorporate the avidin-biotin (first and second members of a binding pair) system to mediate between a reporter group (label) and a primary antibody or antigen (e.g. p. 237). Bayer et al discloses that avidin can be coupled to a reporter to form a conjugate and contacted with biotinylated binding partner (e.g. pgs 250-251, 257-258). Bayer et al also discloses that preformed complexes of avidin and biotinylated probes (e.g. pages 251-255). Bayer et al teaches that the incorporation of the avidin-biotin system improves greatly the performance of the immunoassay system by substantial amplification of the signal and consequent sensitivity of the assay or simply by convenience and provides for a versatile and universally applicable immunoassay system for a given laboratory (e.g. p 237).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the avidin-biotin system with the analyte A-specific binding partner R3 and the label L2 (probe) as conjugates or preformed complexes into the method of Frengen because Bayer et al teaches that the incorporation of the avidin-biotin system improves greatly the performance of the immunoassay system by substantial amplification of the signal and consequent sensitivity of the assay or simply by convenience and provides for a versatile and universally applicable immunoassay system for a given laboratory.

11. Claims 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frengen in view of Buranda et al (Cytometry 37: 21-31, 1999).

See above for the teachings of Frengen.

Frengen differs from the instant invention in failing to teach detection by energy transfer.

Buranda et al teaches that it is known in the art of flow cytometry to incorporate fluorescence resonance energy transfer (FRET) to provide for the determination of K_d values, which indicate agreement between solution and flow cytometric determinations.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate FRET assays as taught by Buranda et al into the method of Frengen because Buranda et al teaches that this provides for the determination of K_d values, which indicate agreement between solution and flow cytometric determinations.

12. Claims 16 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frengen in view of Ullman et al (Proc. Natl. Acad. Sci USA, Vol 91, pp. 5426-5430, 1994).

See above for the teachings of Frengen.

Frengen differs from the instant invention in failing to teach photosensitizers and chemiluminescent substances.

Ullman et al teach particles comprising photosensitizers and chemiluminescent substances utilized in luminescent oxygen channeling immunoassays (e.g. p. 5426).

Ullman et al teaches that this provides real-time measurement of particle binding kinetics (p. 5426).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate photosensitizers and chemiluminescent substances such as taught by Ullman et al into the method of Frengen because Ullman et al teaches that this provides for real-time measurement of particle binding kinetics.

13. Claims 43, 44, 54 and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frengen in view of Bayer et al as applied to claims 1-22, 32-42 and 46-53 above, and further in view of Buranda et al (Cytometry 37: 21-31, 1999).

See above for the teachings of Frengen and Bayer et al.

Frengen and Bayer et al differ from the instant invention in failing to teach detection by energy transfer.

Buranda et al teaches that it is known in the art of flow cytometry to incorporate fluorescence resonance energy transfer (FRET) to provide for the determination of K_d values, which indicate agreement between solution and flow cytometric determinations.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate FRET assays as taught by Buranda et al into the modified method of Frengen because Buranda et al teaches that this provides for the determination of K_d values, which indicate agreement between solution and flow cytometric determinations.

14. Claims 45 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frengen in view of Bayer et al and Buranda et al as applied to claims 1-22, 32-44 and 46-55 above, and further in view of Ullman et al (Proc. Natl. Acad. Sci USA, Vol 91, pp. 5426-5430, 1994).

See above for the teachings of Frengen, Bayer et al and Buranda et al.

Frengen, Bayer et al., and Buranda et al differ from the instant invention in failing to teach photosensitizers and chemiluminescent substances.

Ullman et al teach particles comprising photosensitizers and chemiluminescent substances utilized in luminescent oxygen channeling immunoassays (e.g. p. 5426). Ullman et al teaches that this provides real-time measurement of particle binding kinetics (p. 5426).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate photosensitizers and chemiluminescent substances such as taught by Ullman et al into the modified method of Frengen because Ullman et al teaches that this provides for real-time measurement of particle binding kinetics.

Response to Arguments

15. Applicant's arguments filed 10/27/09 have been fully considered but they are not persuasive.

Applicant argues that Frengen teaches that "the two forms of binding partner are reacted successively rather than simultaneously with the analyte and labeled ligand" (col 3 lines 53-55, col 4, lines 1-4 and col 10, lines 10-15). This argument is not found

persuasive because the instantly recited claims do not exclude the addition of reagents successively. The claim as recited merely requires an incubation of a mixture comprising all of the components and as indicated for example in col 10, lines 1-32 of Fregen (US 5,739,042) the reagents are added to together albeit in successive steps and allowed to incubate. Therefore, Fregen reads on the instantly recited claim.

Applicant argues that Frengen provides no teaching regarding the selection of analyte binding partners based on the concentration or incubation time required to saturate their analyte binding sites. Applicant states that the recitations in column 5 of Frengen reciting "the time interval between reaction with the first and second forms of solid-supported binding partner is not critical provided that it is kept substantially constant for a given assay system" and "since addition of the second form of solid-supported binding partner....effectively quenches reaction of the analyte with the first form of solid-supported binding partner, the process of the invention avoids any need to allow the first form of solid supported binding partner to reach equilibrium with the analyte" do not teach that the selection of analyte binding partners should be based on saturation of their analyte binding sites. This is not found persuasive because although Fregen does not explicitly state the selection of analyte binding partners should be based on saturation of their analyte binding sites. Fregen clearly teaches a substantial excess of the second form of solid-supported binding member (R3) (col 4, lines 52-67 & col 5, lines 30-35) and specifically teaches that the first form of solid binding partner (R2) is supplied in low amount with a maximum of binding member (col 4, lines 43-51).

Therefore, for reasons stated in Fregen the R2 binding member requires a longer incubation time than R3 for saturation of the binding members to the analyte.

Applicant argues that Frengen teaches that the measurement signals are determined at the same time and not at a different time. Applicant argues that Frengen teaches that the measurement signals determined therein, i.e. particle-associated light scatter and fluorescence signals, were measured simultaneously. Thus,, although Frengen's particles may pass through the examination zone individually, the measurement signals are determined at the same time. These arguments are not found persuasive because the particle-associated light scatter and fluorescence signals which are measured simultaneously in Frengen are parameters of the same solid-support complex and not measurements of all beads simultaneously. As shown by Chandler et al during methods of flow cytometry bead subsets are pooled and individual subsets of beads are determined by the parameters of the individual beads (col 4, Chandler et al). Chandler et al col 4, lines 27-67 discloses that at some point prior to assay, the variously labeled subsets are pooled. The pooled beads, or beadset, are then mixed with a fluid sample to test for analytes reactive with the various reactants bound to the beads. The system is designed so that reactions between the reactants on the bead surfaces and the corresponding analytes in the fluid sample will cause changes in the intensity of at least one additional fluorescent signal (F_m) emitted from a fluorochrome that fluoresces at parameters C_3 or C_4. The F_m signal serves as a "measurement signal," that is, it indicates the extent to which the reactant on a given bead has undergone a reaction with it corresponding analyte. The F_m signal may result from the

addition to the assay mixture of fluorescently labeled "secondary" reagent that binds to the bead surface at the site where a reactant-analyte reaction has occurred. When the mixture (pooled beads and fluid sample) is run through a flow cytometer, each bead is individually examined. The classification parameters e.g., C_1, C_2, C_3, and C_4, are measured and used to classify each bead into the subset to which it belongs and therefore, identify the analyte that the bead is designed to detect. The F_m value of the bead is determined to indicate the concentration of analyte of interesting the fluid sample. Not only are many beads from each subset rapidly evaluated in a single run, multiple subsets are evaluated in a sample run. Further, Frengen specifically teaches the two types of particles are separately determined (e.g. col 3, lines 32-35). Thus, for reasons stated above and in the previous office action Fregen reads on the instantly recited claims.

Applicant appears to argue that Buranda does not cure the deficiencies of Frengen. This argument is not found persuasive because of reasons stated above that Frengen in light of Chandler et al reads on the instantly recited claims. Therefore, the rejection based on Frengen in light of Chandler is considered appropriate and the rejections based on the combination of Frengen in view of Buranda et al is maintained.

Applicant appears to argue that Ullman does not cure the deficiencies of Frengen. This argument is not found persuasive because of reasons stated above that Frengen in light of Chandler et al reads on the instantly recited claims. Therefore, the rejection based on Frengen in light of Chandler is considered appropriate and the rejections based on the combination of Frengen in view of Ullman et al is maintained.

Conclusion

16. No claims are allowed.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GARY W. COUNTS whose telephone number is (571)272-0817. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ Gary W. Counts/
Examiner, Art Unit 1641

/Melanie Yu/
Primary Examiner, Art Unit 1641